



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b>  <b>A61K 31/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 00/15205</b>  <b>(43) International Publication Date:</b> 23 March 2000 (23.03.00)
<b>(21) International Application Number:</b> PCT/EP99/06648  <b>(22) International Filing Date:</b> 9 September 1999 (09.09.99)  <b>(30) Priority Data:</b> FI98A000208 11 September 1998 (11.09.98) IT  <b>(71) Applicant (for all designated States except US):</b> EISAI CO., LTD. [JP/JP]; 6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo 112-8088 (JP).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> NICOLODI, Maria [IT/IT]; (IT). SICUTERI, Federigo [IT/IT]; Via Montefiano, 2, I-50014 Fiesole (IT).  <b>(74) Agent:</b> GERVASI, Gemma; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I-20122 Milan (IT).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> USE OF ACETYLCHOLINESTERASE INHIBITORS FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF FUNCTIONAL AND/OR ORGANIC PAIN SYNDROMES  <b>(57) Abstract</b>  The application refers to the use of acetylcholinesterase inhibitors having central action for the treatment of functional (migraine and primary fibromyalgia) and/or organic (amputation, "phantom limb", tumoral or traumatic denervation or autoimmune mechanism) central pain syndromes.		

USE OF ACETYLCHOLINESTERASE INHIBITORS FOR THE PREPARATION  
OF PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF  
FUNCTIONAL AND/OR ORGANIC PAIN SYNDROMES

**Field of the invention**

- 5 The present invention refers to the use of acetylcholinesterase inhibitors with high specificity and selectivity for centrally active acetylcholinesterase (resulting in an increased concentration and duration of acetylcholine in brain) for preparing pharmaceutical compositions for the treatment of functional (migraine and primary fibromyalgia) and/or organic ("phantom limb" caused by tumoral or traumatic  
10 denervation or autoimmune mechanism) central pain syndromes.

**State of the art**

- Along the years migraine has been the object of deep interest and studies in view of the importance of this pathology both for the extremely large number of patients involved and because it causes (during its more serious episodes) important or  
15 total limitations to otherwise healthy subjects.

- Various theories were formulated in order to find an explanation to the origin of migraine. Among these theories we can remember the "dry theory" (according to which the pain is due to the pulsing distension of cephalic vessels), the "wet theory" (which implies the sterile inflammation of the arterial vessels which  
20 became dilated and bloated), the "serotonin-theory" according to which the pathology is caused by a disorder of the serotonergic system in the central nervous system.

- This last theory was very successful and allowed the preparation of active principles having a serotonin-mimetic activity capable of relieving a migraine  
25 attack.

- About thirty years ago an interesting article [Stoyan Iv. IKONOMOFF - Archives Suisses de Neurologie, Neurochirurgie et de Psychiatrie - Vol. 102, fascicule p. 299-312 (1968)] referred to the possibility of treating migraine by using pharmaceutical products, such as Nivaline, an alkaloid, and Syntostigmine, which  
30 were known for their acetylcholinesterase inhibiting effect .

The article proposed the use of the two above said compounds (or more generally

of acetylcholinesterase inhibiting medicaments) as a possible new way for resolving migraine disorders. Unfortunately the use of the medicaments suggested in the above said work, as also of other similar compounds having the same effect, required very high dosages, the administration should be performed by injection and was responsible of various side effects which made their use difficult; therefore this way was abandoned and no indication was thereafter reported in the literature about the use of acetylcholinesterase inhibitors as medicament for the treatment of migraine. In fact even the most recent editions of fundamental text-books in Neurology and Pharmacology [see for example Victor and Adams, McGraw-Hill, New York (last edition) and Goodman and Gilman, McGraw-Hill, New York (1996) respectively] do not report these drugs as employed or useful for treating pain, whatever its origin and mechanism. Moreover in various studies [see for example C. Ghelardini et al. - Presynaptic auto- and hetero-receptors in the cholinergic regulation of pain - Trends in Receptor Research (Elsevier Science Publishers B.V. ) (1992)] it is reported that peripherically active acetylcholinesterase inhibiting compounds are not suitable for analgesic use in man.

#### **Brief description of the drawings**

Fig. 1 shows the number of hours with pain before and after 60 days chronic treatment with Donepezil hydrochloride.

Fig. 2 shows the number of migraine attacks before and after chronic Donepezil hydrochloride treatment.

Fig. 3 shows the number of hours with pain before and after chronic treatment with Donepezil hydrochloride.

Fig. 4 shows the number of migraine attacks before and after Donepezil hydrochloride treatment.

Fig. 5 shows the results of prophylaxis of migraine with Donepezil hydrochloride.

Fig. 6 shows the results of prophylaxis of migraine with Donepezil hydrochloride.

#### **Detailed description of the invention**

It was now surprisingly found that acetylcholinesterase inhibiting compounds with high specificity and selectivity for centrally active acetylcholinesterase can be used

with excellent results in the acute, abortive or preventive, prophylactic treatment of migraine and also of other related disorders which are commonly defined as functional and/or organic neurogenic central pain syndromes.

Furthermore, the acetylcholinesterase inhibiting compounds with high specificity  
5 and selectivity for centrally active acetylcholinesterase in the present invention is defined as follows: the acetylcholinesterase inhibiting compounds having clinical indication of use such as central -progressive memory deterioration in Alzheimer disease or senile dementia and which can cross the blood-brain barrier and can enter the brain in large amounts.

10 Other anticholinesterase agents can not be useful for treating CNS cholinergic disturbances due to acting peripheral tissues including sympathetic ganglia.

Among the above said pathologies we can remember: migraine, primary fibromyalgia, pain syndromes from organic deafferentation caused by amputation ("phantom limb"), denervation or autoimmune mechanism (multiple sclerosis) or  
15 infections (zoster postherpetic neuralgia).

The acetylcholinesterase inhibitors according to the invention as above defined do not present the undesired side effects as miosis and block of accommodation reflex with resultant focusing problems in near vision, changes in the function of all the secretory glands, including lacrimal, bronchial, sweat, salivary, antral, intestinal,  
20 and acinar pancreatic glands, nausea, vomit, gastric acid hyper-secretion, abdominal pains, diarrhoea, fainting or pre-fainting sensation, disturbances of cardio-vascular functions. The administration is well tolerated by patients and allows to obtain the desired results even with a single oral administration daily.

The present invention obviously refers to pharmaceutical compositions containing  
25 as active principle an acetylcholinesterase inhibitor having central activity possibly in combination with the usual excipient used for preparing pharmaceutical composition for oral administration for the treatment of the above said pathologies. In particular the compositions according to the invention will contain the active principle in quantities comprised between 1.5 - 12 mg, more preferably 5 - 10 mg.

30 The treatment can be symptomatic or chronic.

The symptomatic, acute treatment is normally performed by administering orally to

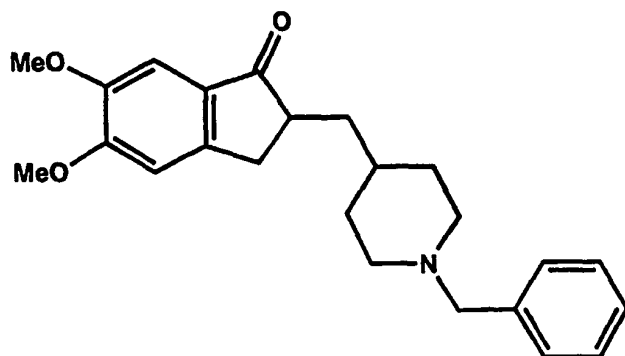
the patient a single dosage containing from 0.1 to 50 mg daily, preferably 0.5 to 40 mg daily, more preferably 1 to 30 mg daily of active principle ; while for the chronic treatment the same administration can be repeated once a day for 40 - 80 days.

Among the compounds useful according to the present invention particularly  
5 preferable are : Donepezil or a pharmacologically acceptable salt thereof,  
Rivastigmine or a pharmacologically acceptable salt thereof and Metrifonate.

These compounds are shown hereinafter:

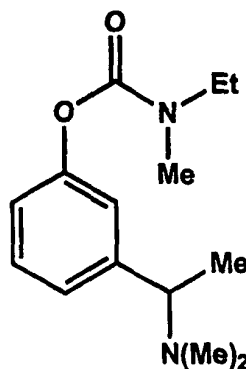
Donepezil

1H-Inden-1-one, 2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-  
10 piperidiny]]methyl]-, hydrochloride  
[Hydrochloride: CAS Registry No. 120011-70-3]



(2) Rivastigmine

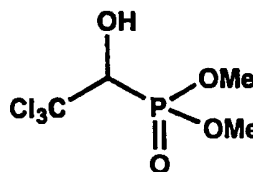
Carbamic acid, ethylmethyl-, 3-[1-(dimethylamino)ethyl]phenyl ester  
15 [CAS Registry No. 123441-03-2]



### (3) Metrifonate

Phosphoric acid, (2,2,2-trichloro-1-hydroxyethyl)-, dimethyl ester

[CAS Registry No. 52-68-6]



5

In the present invention, the term "pharmacologically acceptable salt thereof" include the salts of inorganic acids, such as hydrochloride, hydrobromide, sulfate, nitrate and phosphate, and those of organic acids, such as formate, acetate, oxalate, succinate, maleate, fumarate, methanesulfonate, benzenesulfonate and toluenesulfonate. Among these, hydrochloride is more preferable.

In practising the present invention, the acetylcholinesterase inhibitor compounds of the present invention may be orally or parentally administered. In general, the are administered in the form of tablet, granule, capsule and syrup, and in the form of injection, such as intravenous, subcutaneous and intramuscular injection, suppositories or sublingual tablets.

The dose will vary depending upon the symptom, age, sex, body weight, sensitivity of patients, method of administration, time and interval of administration and property, dispensing, and kind of pharmaceutical preparations, kind of effective ingredients, etc..

Pharmaceutical preparations in the form of, e.g., tablet, granule, capsule, syrup, injections are prepared according to the usual manner.

#### Experimental data

##### Migraines

Various groups of patients suffering from different kind of migraine were treated with 5 mg of Donepezil hydrochloride daily.

The results are reported in the following histograms 1 to 6 (see Figure 1 - 6).

Fig. 1 - Shows the number of hours with pain before and after 60 days chronic treatment with Donepezil hydrochloride (5 mg/die) measured in tests on 17

patients suffering from chronic migraine, otherwise known as "transformed migraine" (International Headache Society criteria).

Fig. 2 - Shows the number of migraine attacks before and after chronic Donepezil hydrochloride treatment (5 mg/die) for the above said group of patients.

5 Fig. 3 - Shows the number of hours with pain before and after chronic treatment with Donepezil hydrochloride (5 mg/die) measured in tests on 18 patients suffering from migraine without aura.

Fig. 4 - Shows the number of migraine attacks before and after Donepezil hydrochloride treatment (5 mg/die) for the same group of patients as in Fig. 3.

10 Fig. 5 - Shows the results of prophylaxis of migraine with Donepezil hydrochloride reporting the number of migraine attacks following 60 days run-in and 60 days treatment in 35 patients suffering from severe migraine without aura.

Fig. 6 - Shows the results of prophylaxis of migraine with Donepezil hydrochloride reporting the hour with pain following 60 days run-in and 60 days treatment for the  
15 same group of patients as in Fig. 5.

Moreover, 8 patients suffering from migraine attacks longer than 72 h were treated with 20 mg of Donepezil hydrochloride acutely given, also in this case the results were highly satisfactory.

#### Primary fibromyalgia

20 Systemic pain of muscles, tendons, viscera (oesophagus, stomach, colon) ; these syndromes are considered particularly difficult to hale.

Tests performed on 16 patents (same conditions as those described for the migraine tests) showed an improvement of the patient's conditions in 60% of the cases treated and total disappearance of the pain in 10% of the cases.

25 Pain syndromes caused by denervation

In the pain syndromes caused by denervation or amputation pain develops on the limb or body part which is denervated and therefore is insensible to nociceptive stimuli ("painful anaesthesia").

Nine patients who had no advantages after treatment with antiinflammatory analgesica or opioids were tested in the same conditions as above described.  
30

Five patients showed an improvement of their conditions of 50 - 80%.

All patients showed an high tolerance to the treatment, with side effects much lower then those observed in the case of administration of the commonly available acute and prophylactic therapies for curing migraine and central neurogenic pain.

## CLAIMS

- 1 1. A use of an acetylcholinesterase inhibitor with high specificity and selectivity for  
2 centrally active acetylcholinesterase for preparing pharmaceutical composition  
3 useful for the treatment of functional and/or organic pain syndromes.
- 1 2. The use according to Claim 1 wherein such functional and/or organic  
2 neurogenic pain syndromes are : migraine, primary fibromyalgia, pain syndromes  
3 due to amputation ("phantom limb"), tumoral or traumatic denervation or  
4 autoimmune mechanism.
- 1 3. The use according to Claim 1 or 2 wherein the active principle is Donepezil or a  
2 pharmacologically acceptable salt thereof.
- 1 4. The use according to Claim 1 or 2 wherein the active principle is Rivastigmine  
2 or a pharmacologically acceptable salt thereof.
- 1 5. The use according to Claim 1 or 2 wherein the active principle is Metrifonate.
- 1 6. A Pharmaceutical composition for the treatment of functional and/or organic  
2 pain syndromes containing an active principle according to Claim 1 in combination  
3 with the pharmaceutically acceptable excipients for the preparation of formulation  
4 for oral use.
- 1 7. The pharmaceutical compositions according to Claim 6 wherein the active  
2 principle is present in quantities comprised between 1 to 30 mg.
- 1 8. A method for the treatment of functional or organic pain syndromes  
2 characterised in that 1 to 30 mg of the active principle are administered to the  
3 patient orally, daily.
- 1 9. The method according to Claim 8 wherein the treatment is relief from pain.
- 1 10. The method according to Claim 8 wherein the treatment is prevention of pain  
2 attack.
- 1 11. The method according to Claim 8 wherein the treatment is chronic and  
2 prolonged for 40 - 80 days.
- 1 12. A method for the treatment of functional and/or organic pain syndromes in  
2 human in need of such treatment which comprises administering a therapeutically  
3 amount of acetylcholinesterase inhibitors with high specificity and selectivity for  
4 centrally activ acetylcholinesterase.

- 1 13. The method claimed in claim 12, wherein acetylcholinesterase inhibitor is  
2 Donepezil or pharmacologically acceptable salt thereof.
- 1 14. The method claimed in either of claim 12 or 13, wherein acetylcholinesterase  
2 inhibitor administered in a daily dose of from 0.1 to 50 mg.
- 1 15. The method claimed in either of claim 12 to 14, wherein acetylcholinesterase  
2 inhibitor administered in a daily dose of from 1 to 30 mg.
- 1 16. A use of acetylcholinesterase inhibitor with high specificity and selectivity for  
2 centrally active acetylcholinesterase for the treatment of functional and/or organic  
3 pain syndrome.

1/3

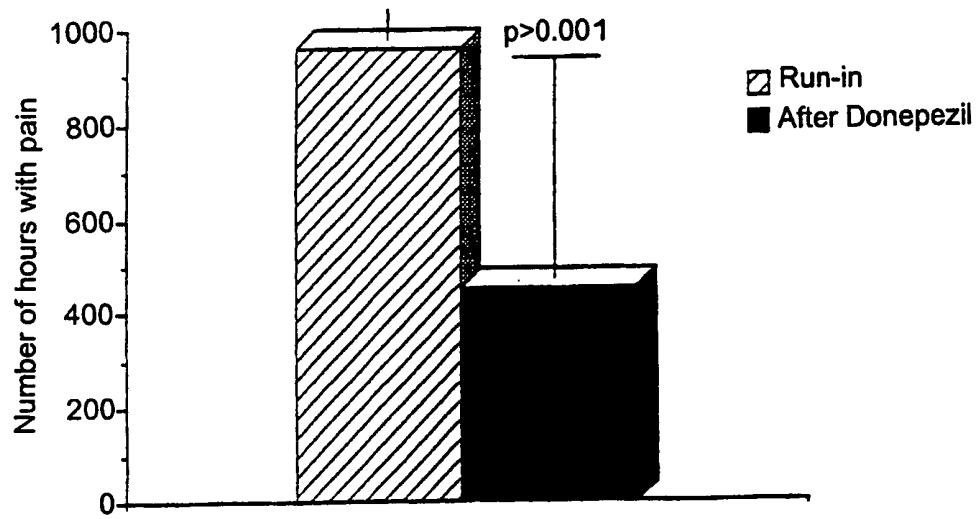


Fig. 1

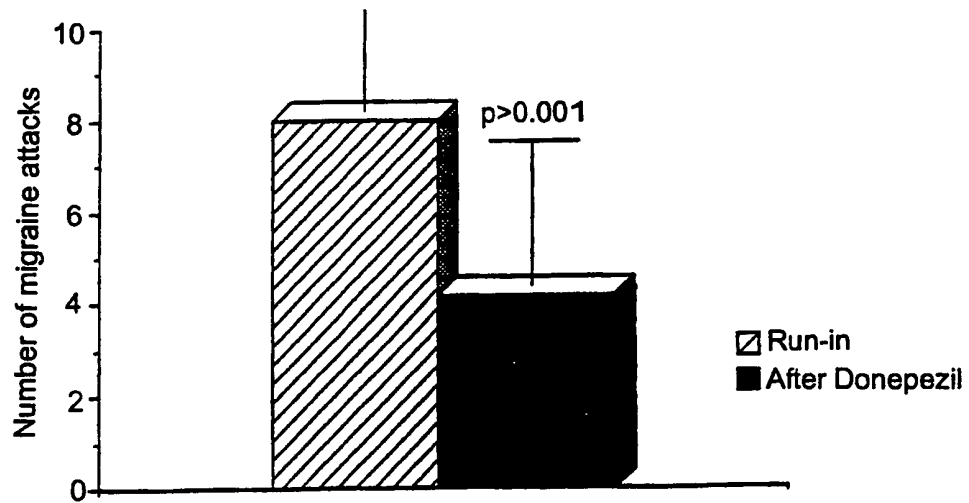


Fig. 2

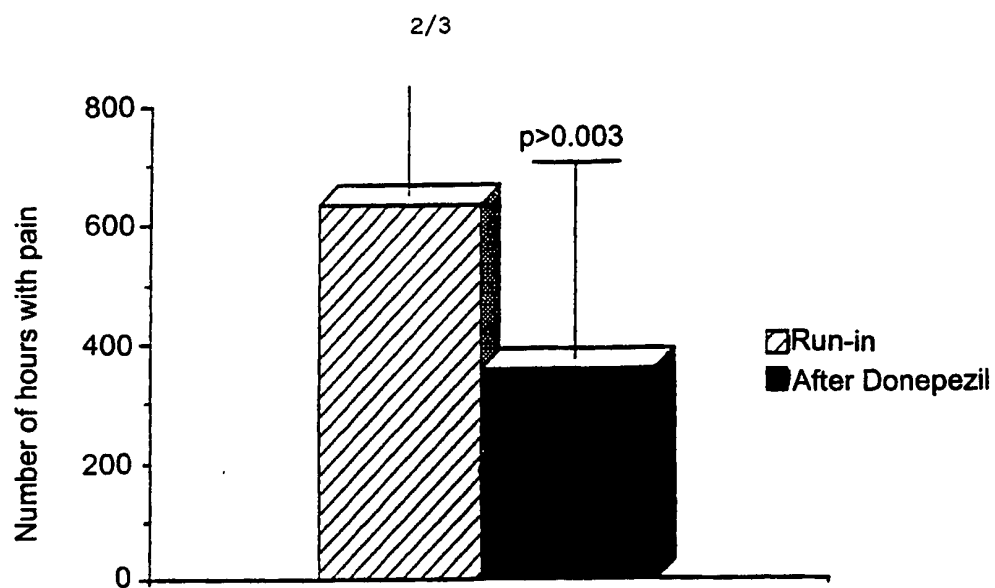


Fig. 3

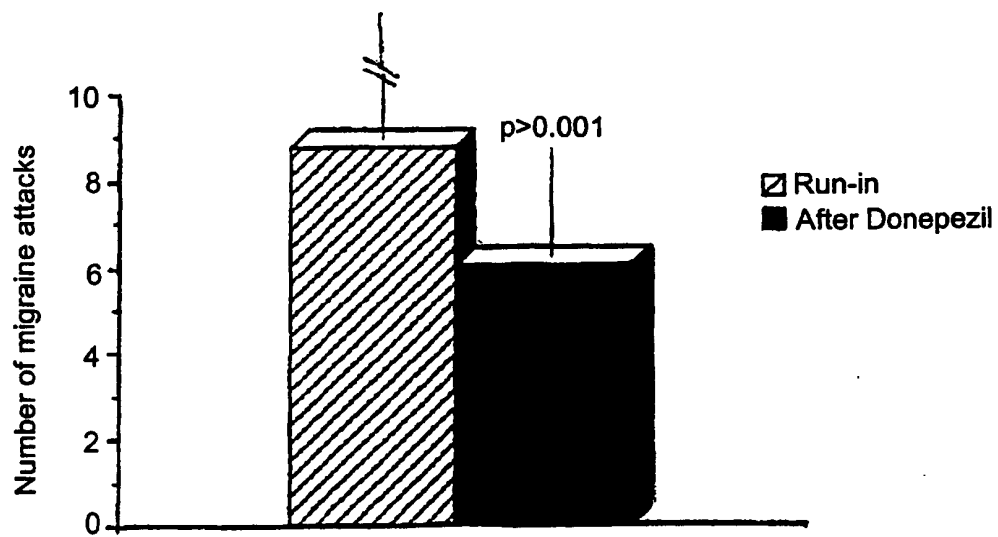


Fig. 4

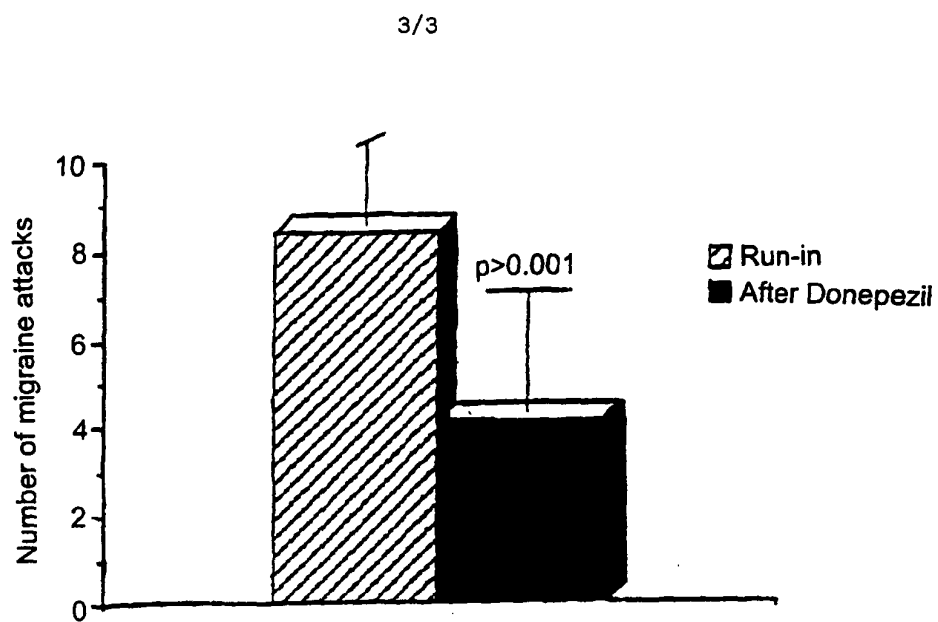


Fig. 5

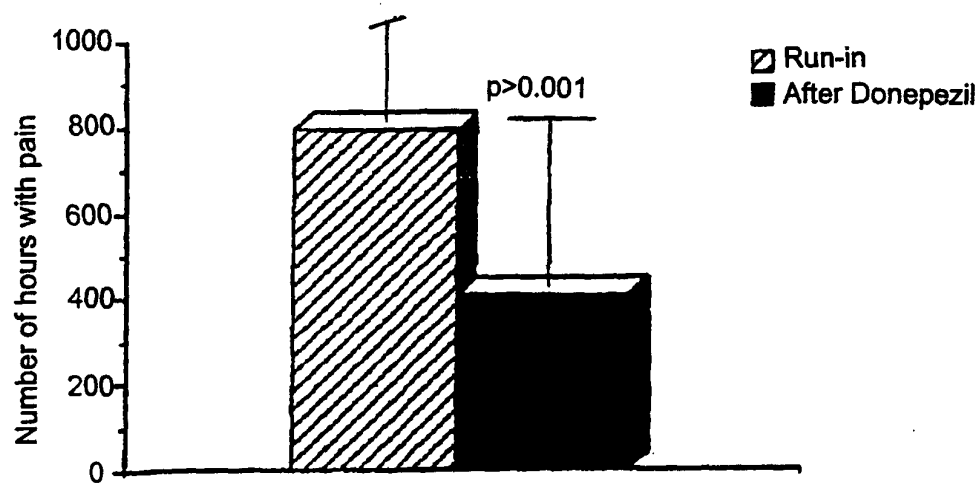


Fig. 6



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 31/00, 31/445, 31/27,</b> <b>31/662, A61P 25/04</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/15205</b>  <b>(43) International Publication Date:</b> 23 March 2000 (23.03.00)
<b>(21) International Application Number:</b> PCT/EP99/06648  <b>(22) International Filing Date:</b> 9 September 1999 (09.09.99)  <b>(30) Priority Data:</b> FI98A000208 11 September 1998 (11.09.98) IT  <b>(71) Applicant (for all designated States except US):</b> EISAI CO., LTD. [JP/JP]; 6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo 112-8088 (JP).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> NICOLODI, Maria [IT/IT]; (IT). SICUTERI, Federigo [IT/IT]; Via Montefi- ano, 2, I-50014 Fiesole (IT).  <b>(74) Agent:</b> GERVASI, Gemma; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I-20122 Milan (IT).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>  <b>(88) Date of publication of the international search report:</b> 24 August 2000 (24.08.00)
<b>(54) Title:</b> USE OF ACETYLCHOLINESTERASE INHIBITORS FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF FUNCTIONAL AND/OR ORGANIC PAIN SYNDROMES		
<b>(57) Abstract</b>  The application refers to the use of acetylcholinesterase inhibitors having central action for the treatment of functional (migraine and primary fibromyalgia) and/or organic (amputation, "phantom limb", tumoral or traumatic denervation or autoimmune mechanism) central pain syndromes.		

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/06648

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/445 A61K31/27 A61K31/662 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 99 08672 A (MURRAY JAMES ROBERT ; SNORRASON ERNIR (IS); SHIRE INTERNATIONAL LIC) 25 February 1999 (1999-02-25)</p> <p>abstract</p> <p>page 5, line 1 - line 31</p> <p>page 7, line 4 - line 11</p> <p>page 7, line 18 - line 21</p> <p>claims 1,6,9,10; examples 6,7,9</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1,3,6-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 March 2000

Date of mailing of the international search report

27.06.00

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/06648

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	NICOLODI M (REPRINT) ET AL: "Migraine prophylaxis by brain cholinesterase inhibitors" INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY, (SEP 1998) VOL. 30, NO. 1-2, SP. ISS. S1, PP. 239-239. PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0167-8760., XP000892200 UNIV FLORENCE, INTERUNIV HEADACHE CTR, I-50121 FLORENCE, ITALY; UNIV FLORENCE, DEPT INTERNAL MED, I-50121 FLORENCE, ITALY abstract 239 ---	1-3,6-16
X	BRYSON, HARRIET M. ET AL: "Donepezil" DRUGS AGING (1997), 10(3), 234-239, XP000900063 whole document, in particular page 237, left-hand column paragraph 3 ---	1,3,6-16
X	DAWSON G R ET AL: "The effects of novel cholinesterase inhibitors and selective muscarinic receptor agonists in tests of reference and working memory." BEHAVIOURAL BRAIN RESEARCH, (1993 NOV 30) 57 (2) 143-53., XP000900038 abstract page 144, right-hand column, last paragraph -page 145, left-hand column, last paragraph; table 1 page 151, left-hand column, paragraph 2 -right-hand column, paragraph 1 ---	1,3,6-16
X	WO 97 29750 A (SNORRASON ERNIR ;MURRAY JAMES (GB)) 21 August 1997 (1997-08-21) abstract page 1, line 25 -page 3, line 10 page 5, line 6 - line 14 page 14, line 6 - line 8; examples 4,5,7 claims ---	1,3,6-16
X	EP 0 515 302 A (SNORRASON ERNIR) 25 November 1992 (1992-11-25)  abstract page 4, line 2 - line 47 page 5, line 23 -page 6, line 49 page 7, line 44 -page 8, line 5; examples 2,5; tables 6.1,6.2 claims --- -/--	1,2, 6-12, 14-16

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/06648

## C.(Continuation) D CUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>IKONOMOFF S I: "[A new method in the treatment of migraine using anticholinesterase drugs (clinical observations)]. Nouvelle methode de traitement de la migraine au moyen de medicaments anticholinesterasiques (observations cliniques)."</p> <p>SCHWEIZER ARCHIV FUR NEUROLOGIE, NEUROCHIRURGIE UND PSYCHIATRIE, (1968) 102 (2) 299-312., XP000892202</p> <p>cited in the application</p> <p>the whole document</p>	1,2,6, 12,16
X	<p>EP 0 413 667 A (SANDOZ LTD ;SANDOZ AG (DE); SANDOZ AG (AT))</p> <p>20 February 1991 (1991-02-20)</p> <p>abstract</p> <p>page 4, line 57 -page 5, line 23; claims 1,6</p>	1,6-12, 14-16
X	<p>US 5 010 083 A (ALLEN RICHARD C ET AL)</p> <p>23 April 1991 (1991-04-23)</p> <p>abstract</p> <p>column 14, line 50 -column 16, line 15</p> <p>column 18, line 22 - line 39; claims 1,26,27</p>	1,6-12, 14-16
X	<p>PRESS J.B. ET AL: "Recent advances in opioid and non-opioid analgesia (1992-1993)."</p> <p>EXPERT OPINION ON THERAPEUTIC PATENTS, (1994) 4/4 (379-393)., XP000892201</p> <p>page 386, left-hand column, paragraph 3</p> <p>-right-hand column, paragraph 1</p>	1,6,12, 16
X	<p>ABRAM, STEPHEN E. (1) ET AL: "Intrathecal acetyl cholinesterase inhibitors produce analgesia that is synergistic with morphine and clonidine in rats."</p> <p>ANESTHESIA &amp; ANALGESIA, (1995) VOL. 81, NO. 3, PP. 501-507., XP000892211</p> <p>the whole document</p>	1,6,12, 16

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 99/06648

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 8-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  

1-2 (partially), 3, 6-12 (partially), 13, 14-16 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-2(partially),3,6-12(partially),13,  
14-16(partially)

Use of Donepezil in relation to the treatment of functional  
and/or organic pain syndromes

2. Claims: 1-2(partially),4,6-12(partially),14-16(partially)

Use of Rivastigmine in relation to the treatment of  
functional and/or organic pain syndromes

3. Claims: 1-2(partially),5,6-12(partially),14-16(partially)

Use of Metrifonate in relation to the treatment of  
functional and/or organic pain syndromes

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1,2,6,7,12,14-16 relate to a compound defined by reference to a pharmacological property, namely "acetylcholinesterase inhibitor with high specificity and selectivity for centrally active acetylcholinesterase" and present claims 8-11 relate to a compound defined by reference to a desirable characteristic or property, namely "active principle for treating pain".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound either by reference to its pharmacological profile or by reference to a result to be achieved (pain treatment). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search for the first subject has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compound structurally identified in claims 3 and 13 (Donepezil), with due regard to the general idea underlying the present invention.

Claims searched completely: 3,13

Claims searched incompletely: 1,2,6-12,14-16

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/06648

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